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EXAMINER	
JUEDES, AMY E	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,055	SAGAWA ET AL.	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,12 and 14-36* is/are pending in the application.

4a) Of the above claim(s) *8 and 14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,12 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 10/11/07, are acknowledged.

Claims 9, 11, and 13 have been cancelled.
Claims 1-8, 10, 12, 28-31, and 33 have been amended.
Claims 34-36 have been added.
Claims 1-8, 10, 12, and 14-36 are pending.

2. Claims 8 and 14-27 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-7, 10, 12, and 28-36 are being acted upon.

3. The rejections of the claims under 35 U.S.C. 112 second paragraph, as outlined in sections A) and D)-I) of the previous office action are withdrawn in view of Applicant's amendment to the claims.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 10, 12, and 31-33 stand rejected, and claims 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth previously, B) Claim 33 recites the limitation "the method for preparing a cytotoxic lymphocyte in the absence of fibronectin" in line 3. There is insufficient antecedent basis for this limitation in the claim, or in independent claim 1.

C) Claim 1 is indefinite in the recitation of a method for "preparing" a cytotoxic lymphocyte comprising the step of "expansion" of a cytotoxic lymphocyte in the presence of fibronectin. It is unclear how a method comprising "expanding" a cytotoxic lymphocyte in the presence of fibronectin results in the preparation of said lymphocyte, in the absence of some type of correlation step.

Applicant's arguments filed 10/11/07 have been fully considered, but they are not persuasive.

Applicant argues that the amendment to the claims obviates

the rejection.

However, claim 33 still lacks antecedent basis, and claim 1 still lacks a step that correlates how "expanding" lymphocytes results in the "preparation" of a lymphocyte.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7, 10, 12, and 28-33 stand rejected, and claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of fibronectin "fragments", or polypeptides having a "substitution, deletion, insertion, or addition to one or more amino acids" of a fibronectin fragment.

As set forth previously, The instant claims encompass employing a genus of fibronectin "fragments" in the claimed method. Fibronectin is a large polypeptide comprising several different domains, including type I, type II, and type III homology repeats. Thus, the instant claims encompass structurally different fibronectin fragments comprising different amino acids sequences corresponding to different fibronectin domains. Additionally, there is no limitation that the claimed fragments even function to stimulate cytotoxic lymphocytes. Indeed, the claims might encompass a fibronectin fragment comprising only 2 amino acids of fibronectin. Likewise, the claims encompass polypeptides comprising a "substitution, deletion, insertion, or addition to one or more amino acids" of the claimed fragments. Said polypeptides would comprise different structures, owing to their unique amino acid sequence. Furthermore, the only functional limitation of the mutated fragments is that they have a "function equivalent" to that of the polypeptides of the claims. However, the claims do not describe what "function" is required. For example, any polypeptide might function as an antigen. Therefore, the claims might encompass mutated polypeptide fragments that are functional equivalents of an antigen. In contrast to the broad range of structurally and functionally different fragments encompassed by the claims, the instant specification only discloses fragments of the type III region of fibronectin. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

Applicant's arguments filed 10/11/07 have been fully considered, but they are not persuasive.

Applicant argues that the claims have been amended to specify fragments having specific sequences, SEQ ID NOS: 1-19, and specific variants with one or more amino acid substitutions.

The claims, as amended, are drawn to a method employing a fibronectin fragment comprising "at least one of the amino acid sequences of" SEQ ID NOS: 1 to 19. This might encompass a broad range of different polypeptides. For example, residues 2-4 of SEQ ID NO: 1 might be considered "one of the amino acid sequences of" SEQ ID NO: 1. Thus, it is not clear that the claims are strictly limited to polypeptides comprising an amino acid sequence selected from the group consisting of the sequences of SEQ ID NO: 1 to 19. Furthermore, the claims encompass fibronectin fragments having one or more amino acid substitutions. This might still encompass structurally different polypeptides with any number of amino acid substitutions. Additionally, as noted above, the recitation of a polypeptide having an equivalent function does not describe what type of function is required of the polypeptide.

7. Claims 1-7, 10, 12, and 28-33 stand rejected, and claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for preparing cytotoxic lymphocytes in the presence of fibronectin or a fibronectin fragment comprising SEQ ID NO: 12,

does not reasonably provide enablement for:

a method for preparing cytotoxic lymphocytes in the presence of a fibronectin fragment, or a fibronectin fragment having a substitution, deletion, insertion, or addition to one or more amino acids.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention,

how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

With regards to the instant claims, their breadth comprises a primary issue as regards the unpredictability of the claimed method. The claims encompass preparing cytotoxic lymphocytes with increased cytotoxic activities, expression of IL-2 receptor, expansion fold, or CD8 ratio comprising inducing, maintaining, or expanding said lymphocytes in the presence of any fibronectin fragment. Fibronectin is 250kDa polypeptide consisting of repeating homology units termed type I, type II, and type III repeats (see Kornblihtt et al., page 248 in particular). It is known that the cell binding and heparin binding domain comprising type III repeats are important in the ability of fibronectin to participate in cell adhesion and growth (see Yoneda et al., page 169-170). However, other fibronectin domains, including the type I repeats, are functionally distinct. For example, some type I domains are involved in binding to the clotting factor fibrin (see Rostagno et al.). It is not clear how said type I fragments could be used to prepare cytotoxic T cell lymphocytes with increased cytotoxic activity, expression of IL-2 receptor, expansion fold, or CD8 ratio, as is encompassed by the instant claims. Additionally, the instant claims encompass employing fibronectin fragments comprising a substitution, deletion, insertion, or addition to one or more amino acids. The only functional limitation of said fragments is that they be "functional equivalents". However, the claims do not specify what function they are required to be equivalent with. For example, the claims might encompass mutated fragments that "function" as an antigen. Thus, the claims might encompass employing any substitution, deletion, or addition, to any amino acid of the claimed fragments, including to regions known to be critical to the function of fibronectin for increasing cytotoxic activity of T cells (for example, the RGD region, see Ostergaard et al.). Thus, given the state of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claims. However, the specification only provides examples utilizing type III fibronectin fragments from the cell binding or heparin binding domain of the polypeptide. Furthermore, the only disclosure of a fragment is a single methionine addition linking various type III fibronectin fragments. This is not commensurate in scope with the instant claims which encompass preparing cytotoxic lymphocytes with any fibronectin fragment, or any substation, addition, or deletion to said fragments. Accordingly, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

Applicant's arguments filed 10/11/07 have been fully considered, but they are not persuasive.

Applicant argues that the claims have been amended to specify fragments having specific sequences, SEQ ID NOS: 1-19, and specific variants with one or more amino acid substitutions.

The claims, as amended, are drawn to a method employing a fibronectin fragment comprising "at least one of the amino acid sequences" of SEQ ID NOS: 1 to 19. This might encompass a broad range of different polypeptides. For example residues 2-4 of SEQ ID NO: 1 might be considered "one of the amino acid

sequences" of SEQ ID NO: 1. Thus, it is not clear that the claims are strictly limited to polypeptides comprising an amino acid sequence selected from the group consisting of the sequences of SEQ ID NO: 1 to 19. Furthermore, the claims encompass fibronectin fragments having one or more amino acid substitutions. However, as noted above, the only functional limitation of said fragments is that they be "functional equivalents". However, the claims do not specify what function they are required to be equivalent with. For example, the claims might encompass mutated fragments that "function" as an antigen. Thus, the claims might encompass employing any number of substituted fragments, including to regions known to be critical to the function of fibronectin for increasing cytotoxic activity of T cells.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 10, 12, and 28-33 stand rejected, and claim 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Pollok et al., 1998.

As set forth previously, Pollock et al. teach a method of transducing T lymphocytes comprising culturing said T lymphocytes in the presence of a fibronectin fragment designated CH-296 (i.e. a method comprising "inducing" or "maintaining" in the presence of fibronectin, see page 4883 in particular). Said T lymphocytes comprise CD8+ T cells (i.e. a cytotoxic lymphocyte, see page 4884 in particular). Furthermore, the instant specification discloses on page 12 that CH-296 is a fibronectin fragment comprising SEQ ID NO: 12. Pollock et al. also teach immobilizing the fibronectin to the surface of a tissue culture plate and culturing the cells at a concentration of 0.5×10^6 cells in 2.8 ml of medium (i.e. at 1.78×10^5 cells/ml), see page 4883 in particular. Furthermore, the tissue culture plate has not been exchanged during the transduction in the presence of fibronectin (see page 4883 in particular). Pollock et al. also teach that the T cells are transduced with a foreign gene using a retroviral vector (see page 4883 in particular). Furthermore, Pollock et al. must have inherently obtained higher expression of IL-2 receptor, a higher ratio of CD8-positive cells, higher maintenance of cytotoxic activity, and higher expansion fold of the T lymphocytes, since they have performed the steps of the claimed method.

Applicant's arguments filed 10/11/07 have been fully considered, but they are not persuasive.

Applicant argues that Pollok et al. do not disclose "expanding" lymphocytes in the presence of fibronectin.

The instant specification on page 11 discloses that the method of producing a cytotoxic lymphocyte by expansion of a cell is also referred to as "culture" of a cytotoxic lymphocyte. Additionally, the instant specification discloses on pages 34-35 that the expansion step is not limited, so long as fibronectin exists in the culture system, for example, by adding it to the medium used in the culture. Pollock et al. teach expanding T lymphocytes with anti-CD3 antibodies, followed by culturing (i.e. expanding) said lymphocytes with fibronectin. Thus, Pollock et al. have "expanded" the lymphocytes in the sequential presence of both fibronectin and anti-CD3 antibody.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 10, 12, 28-30, and 33 stand rejected, and claims 34-35 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Ostergaard et al., 1995, in view of U.S. Patent 5,198,423, as evidence by Nunclon product information.

As set forth previously, Ostergaard et al. teach a method of increasing degranulation of cytotoxic cells comprising culturing a cytotoxic T lymphocyte in the presence of anti-CD3 and purified cellular fibronectin (i.e. a method of preparing a cytotoxic lymphocyte comprising "induction", "maintenance" or "expansion" of said lymphocyte in the presence of fibronectin), see page 253-254 in particular. Ostergaard et al. further teach that the fibronectin is immobilized on a tissue culture plate (see page 253 in particular). Ostergaard et al. also teach that the cells are incubated at a concentration of 10^5 cells/well of a single 96 well Nunclon plate (i.e. without exchanging "cell culture equipment"). As evidenced by the product information for Nunclon plates, this corresponds to a ratio of ~2.8 to 3 x 10^5 cells/cm2. Ostergaard et al. also teach that the ability of fibronectin to increase cytotoxic activity is mediated by the RGD sequence of the polypeptide (see page 255 in particular). Ostergaard et al. also teach that the presence of fibronectin results in an increase in degranulation (i.e. a cytotoxic activity) compared to cytotoxic lymphocytes cultured in the absence of fibronectin (see Fig. 1 in particular).

Ostergaard et al. do not teach a fibronectin fragment comprising SEQ ID NO: 12, or immobilizing the fibronectin on a petri dish, flask, or bag.

The '423 patent teaches a biologically active recombinant fibronectin fragment comprising SEQ ID NO: 12 (see columns 3-4 in particular). The '423 patent also teaches that the recombinant fibronectin fragment comprises a cell binding domain comprising the RGD sequence (see column 1 and 3, in particular). The '423 patent also teaches that the recombinant fibronectin is advantageous compared to natural

fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses (see column 1 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinant fibronectin fragment taught by the '423 patent, for the natural fibronectin in the method of increasing degranulation of cytotoxic T lymphocytes taught by Ostergaard et al. The ordinary artisan at the time the invention was made would have been motivated to do so, since the '423 patent teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the recombinant fibronectin fragment, since Ostergaard et al. teach that the increase of cytotoxic activity is mediated through the RGD sequence of fibronectin, and the '423 patent teaches that the recombinant fibronectin is a biologically fragment comprising an RGD sequence. Additionally, it would have been obvious to culture the cytotoxic T lymphocytes in a petri dish, a flask, or a bag, since these are all well known and routine vessels used for performing tissue culture. Furthermore, the method made obvious by Ostergaard et al. and the '423 patent would result in the increase in IL-2 receptor expression, an improved CD8-positive ratio, and higher expansion fold of cytotoxic lymphocytes, since the references make obvious all the method steps of the instant claims.

Applicant's arguments filed 10/11/07 have been fully considered, but they are not persuasive.

Applicant argues that that Ostergaard et al. only disclose culturing the CTL for 4 hours in the presence of anti-CD3 antibody and fibronectin, and that as such no "expansion" of cytotoxic lymphocytes as in the present invention is carried out.

The instant claims are not limited to "expansion" of lymphocytes for a particular period of time. The cited references make obvious all the steps of the claimed method, and would result in "expansion" of cytotoxic lymphocytes, as claimed. Furthermore, as noted above, the specification clearly indicates that the "expansion" step encompasses merely culturing lymphocytes together with fibronectin.

Applicant further argues that the references do not disclose an increase in IL-2 receptor expression nor an improved CD8 T cell ratio.

However, the references make obvious all of the steps of the claimed method, and therefore would result in the increase IL-2 receptor expression and an improved CD8 ratio. Applicant's further characterization of the method made obvious by Ostergaard et al. and the '423 patent (i.e. that it results in enhanced IL-2 receptor expression or increased CD8 ratio) does not render the instant claims patentable.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-7, 10, 12, and 28-33 stand provisionally rejected, and claims 34-36 are provisionally rejected, on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-8, 14-15, 24-25, and 28 of copending Application No. 10/486,512 in view of U.S. Patent 5,198,423 and Chen et al., 1994.

As set forth previously, The '512 application claims a method for inducing cytotoxic T cells, a method for maintaining cytotoxic T cells, and a method for expanding cytotoxic T cells comprising incubating said T cells with fibronectin or a fragment thereof. The '512 application further claims that said fragment comprises at least one of a VLA-4, VLA-5, and a heparin binding domain. It would have been obvious to use the recombinant fibronectin fragment of the '423 patent (i.e. a fragment comprising SEQ ID NO:12) as the fragment claimed in the '512 application, since the '423 patent teaches that the biologically active fragment is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses. Furthermore, the limitations of the instant claims where the fibronectin is immobilized on a substrate, wherein the concentration of cells is between 1 cell/ml to 5 x 10^5 cells per ml, and wherein the

method excludes an equipment exchange represent obvious variations of the method claimed in the '512 application. Moreover, it would have been obvious to transfect the cytotoxic T lymphocyte with a foreign gene, since Chen teaches that transfection with PKC allows long term growth of cytotoxic T cells in vitro.

This is a provisional obviousness-type double patenting rejection.

12. Claims 1-7, 10, 12, and 28-33 stand provisionally rejected, and claims 34-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 20-21 of copending Application No. 10/568,745.

As set forth previously, The '745 application claims a method for preparing a cytotoxic lymphocyte comprising the step of carrying out at least one step selected from induction, maintenance, and expansion of a cytotoxic lymphocyte in the presence of fibronectin or a fragment thereof. The '745 application further claims that the fibronectin fragment comprises SEQ ID NO: 13, which is the same as SEQ ID NO: 12 of the instant application. The '745 application also claims that the fibronectin is immobilized on a substrate, that the concentration of cells is between 1 cell/ml to 5 x 10^5 cells per ml, and that the method excludes an equipment exchange. The '745 application also claims that the lymphocytes can be transfected with a foreign gene using a retrovirus, adenonvirus, or simian virus.

This is a provisional obviousness-type double patenting rejection.

Applicant's request that the provisional obviousness-type double patenting rejections be reconsidered at the time of allowance is acknowledged.

13. The following are new grounds of rejection necessitated by Applicant's amendment

14. Claims 1-7, 10, 12, and 28-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1 and 28-30 are indefinite in the recitation of a polypeptide having a substitution of one or more amino acids "within each of the groups of: a) glycine, alanine; b) valine, iosleucine, leucine….". As an initial matter, it is unclear how a polypeptide might comprise only one substitution, if the claim further requires a substitution in each of groups a)-f). Additionally, it is not clear what type of substitutions the claims encompass. For example, in a), are the claims intended to encompass a substitution of any glycine or alanine, or are the claims intended to mean that glycine is substituted with alanine?

B) Claim 33 is indefinite in the recitation of an "expansion ratio" of the cytotoxic lymphocyte being high compared to the method of preparing a cytotoxic lymphocyte in the absence of fibronectin. It is not clear if the claim requires that the cytotoxic lymphocyte actually expand as a result of the claimed method, or whether "expansion ratio" refers to a property of the cytotoxic lymphocyte (i.e. an increased potential for expansion).

15. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A method comprising expanding a lymphocyte for "between 2 to 15 days (Claim 36).

Applicant indicates that support for the new claim can be found on pg. 35, lines 16-18.

The instant specification discloses on pg. 35 that LAK cells may be cultured with IL-2 and a fibronectin fragment of the invention for 2 to 15 days. However, this has a different scope than the instant claims, which encompass expanding any cytotoxic lymphocyte in the presence of a fibronectin fragment alone for 2 to 15 days.

16. Claims 1-7, 10, 12, 28-30, and 33-36 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Mizobata et al., 1996, in view of U.S. Patent 5,198,423 (both of record).

Mizobata et al. teach a method comprising expanding PBMC in the presence of anti-CD3 antibodies and human fibronectin (see page 1599 in particular). Mizobata et al. teach that the fibronectin is immobilized on a tissue culture plate (i.e. a "vessel", see page 1599 in particular). Mizobata et al. also teach that the cells are expanded at a concentration of 5×10^5 cells/ml (see page 1599 in particular). Mizobata et al. also

teach that the expansion with fibronectin results in increased numbers of cytotoxic lymphocytes, some of which express CD8 (i.e. an increase in the number of CD8 positive cells, see page 1600 and Table IV, in particular). Mizobata et al. also teach that the fibronectin expanded cytotoxic lymphocytes have improved cytotoxic activity (see page 1600 in particular). Mizobata et al. also teach expanding the cytotoxic lymphocytes for 3 days (see page 1599 in particular). Mizobata et al. also teach that the fibronectin can result in increased expression of CD8 and IL-2 receptor (see Table IV, patient 8 had 1.4% CD8 positive cells with anti-CD3 alone, compared to 12% CD8 positive with CD3 and fibronectin, and patient 5 on day 21 had 57% IL-2 receptor positive cells with anti-CD3 compared to 62% IL-2 receptor positive with anti-CD3 and fibronectin).

Mizobata et al. do not teach a fibronectin fragment comprising SEQ ID NO: 12, or immobilizing the fibronectin on a petri dish, flask, or bag.

The '423 patent teaches a biologically active recombinant fibronectin fragment comprising SEQ ID NO: 12 (see columns 3-4 in particular). The '423 patent also teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses (see column 1 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinant fibronectin fragment taught by the '423 patent, for the human fibronectin in the method of preparing cytotoxic lymphocytes taught by Mizobata et al. The ordinary artisan at the time the invention was made would have been motivated to do so, since the '423 patent teaches that the recombinant fibronectin is advantageous compared to natural fibronectin, which is limited in supply, costly to produce, and potentially contaminated with bacteria and viruses. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the recombinant fibronectin fragment, since the '423 patent teaches that the recombinant fibronectin is a biologically fragment. Additionally, it would have been obvious to culture the cytotoxic lymphocytes in a petri dish, a flask, or a bag, since these are all well known and routine vessels used for performing tissue culture.

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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12/12/07

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER